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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,324	10/17/2005	Roger R. C. New	117-564	9059

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EXAMINER	
KHANNA, HEMANT	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,324	NEW, ROGER R. C.	
	Examiner	Art Unit	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/03/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's request for reconsideration of the application in the Remarks filed January 03, 2007 is found persuasive. Cancelation of the original claim set 1-29, and the addition of new claims 30-58, that read on the original claim set is acknowledged. The Applicant has reformatted the previously presented "use" claims to read on the statutory subject matter of method claims 48-55.

The applicant's arguments pertaining to the rebuttal of the general lack of unity inventive finding made by the Examiner is found persuasive. Based on the Applicant's arguments the Examiner has rejoined the method claims.

Claims 30-58 are pending.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 30-41, 45-52, 56-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, claims 30-41, 45-52, 56-58 recite a broad genus of compounds comprising an "active macromolecular principle" further comprising polypeptides, polynucleotides and polysaccharides taken in combination with an aromatic alcohol and a solubilization aid. While structural limitations or specific functional limitations of the "genus" represented by "polypeptides" in combination with aromatic alcohols and solubilization aids are provided, no structural limitations are provided of the genus represented by polynucleotides or polysaccharides in combination with aromatic alcohols and solubilization aids. Further it is not clear what activity is required of the pharmaceutical composition comprising the "active macromolecular principle". What is the disease that is being treated by the administration of the "active macromolecular principle"? How do these activities/diseases correlate with the structure of the "active macromolecular principle" that is administered?

The specification discloses a long list of "polypeptides", and "polynucleotides" whose structures appear to vary greatly. While some of the substances such as calcitonin, and insulin are quite specific, others such as "proteins which are able to cause replication", are a broad genus that is unclear. Among the polynucleotides, while

nucleotides that encode for a cytokine such as IL-1 is quite specific, others such as polynucleotides that encode an extracellular protein, are a broad genus that is unclear.

As discussed above, there does not appear to be any core structure present in the "active macromolecular principle", or the disclosure of a specific structure that will give rise to an intended activity. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Therefore, the inventor, at the time the application was filed was not in possession of the broad genus comprising the "active macromolecular principle" taken in combination with an aromatic alcohol and solubilization aid needed to practice the claimed invention. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

4. Claim 56 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for methods to treat diabetes by the administration of a pharmaceutical composition comprising insulin, an aromatic alcohol chosen from BHT, BHA or propyl gallate, and a bile salt, does not reasonably provide enablement for the methods to any and all diseases mediated by all compounds of the "active macromolecular principle". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claim 56.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Nature of the invention. The instant invention is to methods for treatment of a condition or disease treatable by the administration of a pharmaceutical composition comprising an "active molecular principle" and an aromatic alcohol chosen from BHT, BHA and analogs and derivatives thereof.

Breadth of the claims. According to the language of the claims, the scope of the method of treatment can be extrapolated to any and all diseases at all times in presence of an "active macromolecular principle". The specification does not disclose a reasonable correlation between the treatment of a disease mediated by compounds other than the insulin.

State and un/predictability of the prior art. The claimed subject matter is lacking in predictability. While examples in the art exist for the treatment of diabetes with the administration of an active macromolecular principle, such as insulin, the art is unpredictable for the treatment of any and all diseases by the administration of polynucleotides. Specifically, Read (2002) teaches that the treatment of cancer via gene therapy remains an elusive goal (abstract). The teachings of the prior art are being interpreted by the fact that the treatment of cancer via the administration of polynucleotides is not a viable option. In view of the above teachings a person of skill in the art would have no evidence that treatment of cancer by a non-proteinaceous "active macromolecular principle" has any basis. It is presumed that the Applicant's intent is to treat diabetes with the administration of insulin, using a composition wherein the

absorption of insulin is enhanced in the presence of hydrophilic alcohols such as BHT or BHA. Since the treatment of cancer by gene therapy is not viable, the treatment of a patient for any and all diseases by the administration of an active macromolecular principle comprising polynucleotides, is not enabled.

Working examples. No examples are disclosed in the specification wherein a composition comprising both an active macromolecular principle and an aromatic alcohol is administered for the treatment of a disease. While an example exists for the increased permeability of aromatic alcohols across intestinal membranes, there is no evidence for the intended permeability of the "active macromolecular principle" specific to the treatment of any or all diseases.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods to extrapolate the methods of treating any and all diseases with an "active macromolecular principle" from the method increased permeability of an aromatic alcohol. There is a lack of predictability in the art regarding the use of an active macromolecular principle for the treatment of any disease.

Amount of experimentation necessary. Given the unpredictability of the art in view of the use of polynucleotides for the treatment of any and all diseases, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate with the scope of the claim. Although the applicants have identified an interesting method of increasing the permeability of proteinaceous compounds, but essentially all of the work required to extrapolate the treatment of a patient needs to be further undertaken.

Relative Skill of those skilled in the art. In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a Ph.D. with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is Ph.D. predictability of the results is not invariable.

In consideration of each of the factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 30-58 rejected under 35 U.S.C. 103(a) as being unpatentable over New (WO 02/28436) in view of New (USPN 5,853,748), Chakravorty (WO 02/022158) and Ivanovic (Chromatographia (1995) 40:652-656).

The instant claims are drawn to pharmaceutical compositions comprising an active molecular principle, an aromatic alcohol, a solubilization aid, and methods of enhancing the absorption of an active macromolecular principle comprising administering to a patient the above-mentioned pharmaceutical composition.

With respect to the composition claims 30-45, 57-58, New ('28436) disclose compositions for oral administration comprising a macromolecule, such as insulin (Example 1) or heparin, further comprising an aromatic alcohol, such as benzyl alcohol (Example 1), wherein the comprises comprises upto 75% by weight of the aromatic alcohol (page 7, lines 25-30). New ('28436) also discloses solubilization aids such as amphiphiles (page 8, lines 15-20) to improve the solubility of the macromolecule in the aromatic alcohol. Further New ('28436) disclose that the compositions of active principal, alcohol and amphiphile can be co-dissolved in the aqueous phase or the water removed by lyophilization (page 10, lines 1-5). In addition New ('28436) disclose enteric capsule of the composition of the invention to withstand the conditions of the stomach, wherein the enteric becomes permeable at a pH from 5.5 to 7 (page 7, lines 10-15).

With respect to the method claims 46-56, New ('28436) discloses methods to treat a patient with a disease that comprises the administration of the above-mentioned composition, wherein the composition enhances the absorption of the active principal across the intestinal walls (claims 26-28).

New ('28436) differs from the instant claims by not explicitly reciting that the aromatic alcohol is selected from butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA), and propyl gallate.

With respect to claims 30-58, Chakravorty discloses that it is known in the art to formulate immunosuppressive drugs with BHT, propyl gallate or benzyl alcohol wherein such agents are antioxidants, and preservatives respectively (page 6, lines 25-30).

With respect to claims 30-58, New ('748) disclose that it is known in the art that compositions that buffer the pH of the digestive tract enhance the absorption of proteinaceous materials (abstract, claim 1). New ('748) disclose the presence of sodium bicarbonate in compositions alongside bile salts and proteinaceous materials, for methods to enhance permeation in the gut (claim 18).

With respect to claims 30-58, Ivanovic disclose that it is known in the art that preservatives and antioxidants such as BHT exhibit pKa's in the range 7.5 to 9. Further, Ivanovic disclose that the ratio of the amounts of ionized antioxidant to unionized antioxidant determines the final pH of the solution.

In view of the above teachings, it would have been obvious to one of ordinary skill in the art to substitute the benzyl alcohol in the formulation of New ('28436) with BHT or BHA, for the known and expected result of proving a means recognized in the art for adjusting the intestinal milieu to enhance the absorption of proteinaceous materials.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hemant Khanna Ph.D.
February 07, 2007

B. DELL CHISM
PRIMARY EXAMINER